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Review article

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Insulin resistance in type 2 diabetes mellitus

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Abstract

Insulin resistance is an integral pathophysiological feature of type 2 diabetes mellitus. Here, we review established and emerging cellular mechanisms of insulin resistance, their complex integrative features and their relevance to disease progression. While recognizing the heterogeneity of the elusive fundamental disruptions that cause insulin resistance, we endorse the view that effector mechanisms impinge on insulin receptor signalling and its relationship with plasma levels of insulin. We focus on hyperinsulinaemia and its consequences: acutely impaired but persistent insulin action, with reduced ability to lower glucose levels but preserved lipid synthesis and lipoprotein secretion. We emphasize the role of insulin sensitization as a therapeutic goal in type 2 diabetes mellitus.

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Key points

- Insulin resistance is, along with β-cell failure, the defining feature of type 2 diabetes mellitus.
- Treating insulin resistance can prevent, treat and reverse type 2 diabetes mellitus, but aside from lifestyle modifications, clinical use of insulin sensitizers has almost ceased.
- Insulin action is understood at a genetic, molecular, biochemical and integrative physiological level in painstaking detail.
- Existing information should enable development of disease-modifying therapies for type 2 diabetes mellitus.
- The fundamental conundrum of insulin sensitization is that it cannot be separated from weight gain and increased lipid and lipoprotein production.
- We discuss future prospects for achieving selective insulin sensitization by selective inhibition of FOXO1 or activation of PPARγ.

Introduction

Insulin resistance precedes the clinical manifestations of type 2 diabetes mellitus (T2DM) and increases in severity after the onset of the disease owing to declining pancreatic β-cell function and the adverse effect of hyperglycaemia[1]. A harbinger of insulin resistance is hyperinsulinaemia, which is a result of increased insulin secretion by β-cells and impaired insulin clearance due to downregulation of insulin receptors on the surface of target cells[2]. Fasting hyperinsulinaemia is as close to a universal marker of insulin resistance and predictor of T2DM as we have[3]. The inverse relationship between levels of insulin and insulin action was recognized in the 1970s with the discovery of ligand-induced insulin receptor internalization[4]. There is a fundamental misconception that increased levels of insulin increase insulin action[5]. On the contrary, hyperinsulinaemia blunts the acute insulin signalling that induces glucose disposal (normally by increasing glucose uptake into tissues and decreasing glucose production), while promoting persistent low-level signalling that principally affects lipid synthesis and storage, as well as lipoprotein metabolism[6]. Indeed, when insulin resistance is treated with insulin sensitizers such as thiazolidinediones, levels of insulin fall, which attests to the compensatory nature of hyperinsulinaemia[7]. However, levels of insulin also fall during the progression of diabetes mellitus due to β-cell dysfunction, a topic we reviewed in 2023 (ref. 8).

In the past 30 years, several new diabetes mellitus treatments have been introduced into medical practice[8] (Fig. 1). Considerable improvements have been made in preventing macrovascular disease and achieving medically effective weight loss[9]. However, the percentage of people with diabetes mellitus enrolled in the National Health and Nutrition Examination Survey achieving target levels of HbA_{1c}, after steadily rising in the late 1980s to the early 1990s, has remained almost unchanged for the past two decades[10]. In addition, insulin sales are forecast to climb from about US $44 billion in 2021 to about $70 billion in 2030 (ref. 11), hardly a sign that alternative treatments are replacing insulin. Possible reasons for these conflicting findings include rising cost of medications and secondary drug failures (which leave a vast unmet need and serious complications)[12], as well as poor prescription adherence[13–15].

Insulin sensitizers such as PPARγ agonists are effective and have longer-lasting effects than other diabetes mellitus treatments that have been developed within the past 30 years[7]. PPARγ agonists also have direct beneficial effects on insulin-producing β-cells[16] and preventative effects against macrovascular disease[17,18]. However, they have all but been phased out of clinical use over concerns about precipitating heart failure, bone loss, weight gain and cancer[19]. Although insulin sensitizers are often conflated with PPARγ agonism, this is not the only mechanism to increase insulin sensitivity. In this Review, we focus on promising future approaches to this problem that make use of selective insulin sensitizers, which can uncouple the glucose-lowering effect of insulin from the lipogenic actions of insulin according to findings from preclinical studies[20,21]. Readers interested in PPARγ agonists are referred to a 2023 review[22].

Mechanisms underlying insulin signalling

Introduction to insulin signalling

Insulin action is conceptually simple (Fig. 2 and Box 1). There is a single ligand (insulin) and a single, ubiquitous cell surface receptor tyrosine kinase[23]. Unlike other tyrosine kinases, it exists as a preassembled homodimer[24]. Cryogenic electron microscopy data indicate that the receptor can bind up to four insulin molecules[25], but a single molecule can trigger full activation[26]. Insulin binding causes a conformational change that allows lysine-1030 in the β subunit to bind ATP and allosterically activate the tyrosine kinase[27]. The tyrosine phosphorylation signal is transduced via four adaptor proteins named insulin receptor substrates (IRS1–4) to activate the lipid kinase phosphoinositide 3-kinase (PI3K)[28], which in turn activates the serine–threonine kinase AKT[29].

AKT family kinases convey the insulin signal to biological effectors that include other kinases, transcription factors, metabolic enzymes, transporters, cell cycle regulators and apoptosis regulators, as well as sundry other mediators of insulin function[24]. A convenient if simplistic explanation for the signalling interactions downstream of AKT (Fig. 2) is that FOXO1, FOXO3a and FOXO4 mediate transcriptional events[30,31], TBC1D4 mediates translocation of GLUT4 vesicles in muscle and adipose cells[32,33], and different enzymes (for example, glycogen synthase kinase 3, ATP citrate lyase, glyceraldehyde phosphate dehydrogenase, phosphodiesterase 3b, phosphofructokinase (also known as fructose bis-phosphatase)) regulate glycolysis and lipolysis. The AKT substrates mTOR, S6K and AMPK regulate protein translation[34] as well as SREBF1-dependent lipogenesis[35]. Anti-apoptotic regulators and cell cycle regulators mediate the modest growth-promoting effects of insulin[36] and endothelial nitric oxide synthase mediates some of insulin's effects on the vasculature[37]. The paramount role of AKT in insulin action is confirmed by loss-of-function mutations in humans[38] and animals[39]. Insulin also activates the MAP kinase pathway, although with notable differences in the mode of activation. The increase in MAP kinase activity in response to insulin is fairly modest, requires elevated doses of insulin[40] and is dissociated from insulin's metabolic actions[41]. This pathway is primarily related to insulin's growth-promoting effects[36].

Termination of insulin signalling

Unrestrained insulin action can cause hypoglycaemia, as seen in patients with insulin-secreting tumours[42], hence the requirement to terminate the insulin signal in different, redundant ways (Fig. 3). The receptor is internalized, becoming unavailable to further stimulation[43]; tyrosine phosphatases remove phosphate from tyrosine residues, ending the engagement of downstream components, and lipid phosphatases terminate the engagement of PI3K[44]. A heterogeneous host of

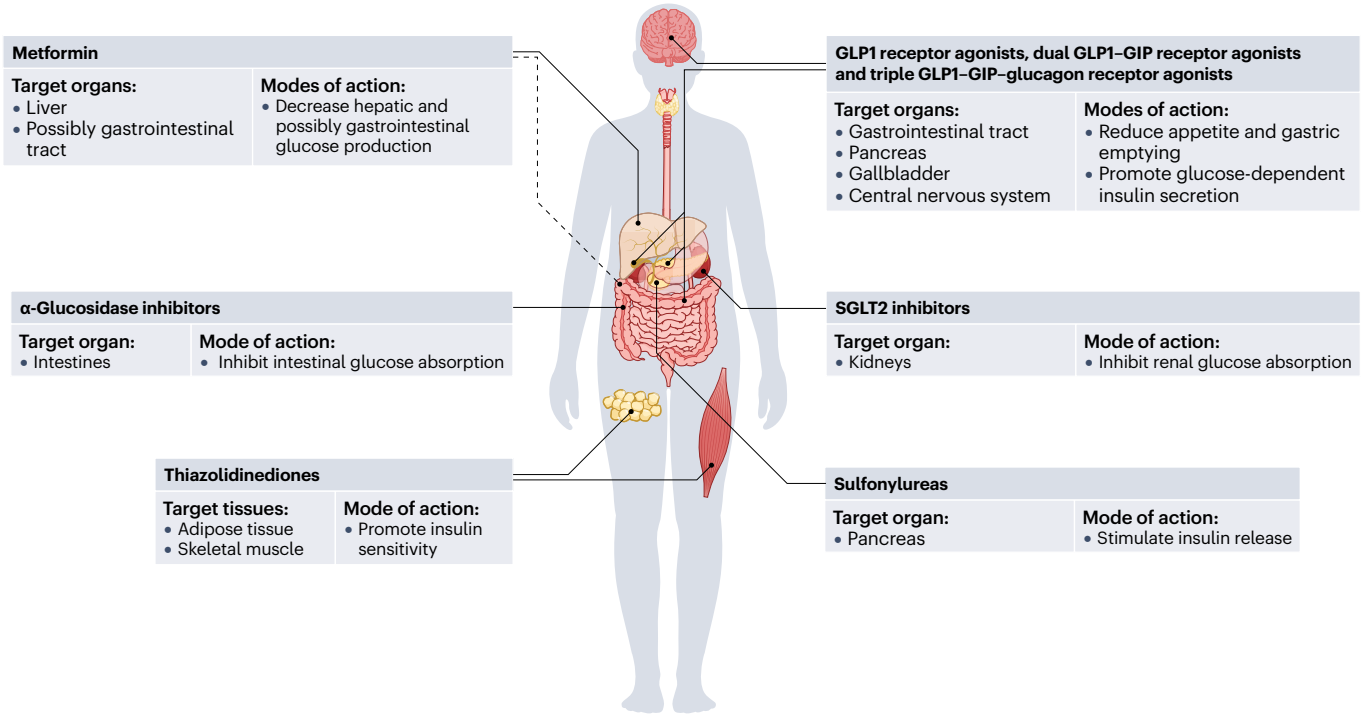

Fig. 1 | Modes of action of antidiabetic treatments. Different antidiabetic drugs exert their actions in mechanistically distinct ways. Metformin reduces hepatic and possibly gastrointestinal glucose production, and probably has multiple molecular targets. α-Glucosidase inhibitors reduce intestinal glucose absorption. Thiazolidinediones affect multiple target organs, promoting insulin sensitivity and lipid accumulation, with important secondary effects on bone, heart and kidney. Sulfonylureas inhibit the β-cell K_{ATP} channel, thus promoting insulin secretion. Glucagon-like peptide 1 (GLP1) receptor agonists target a different, cAMP-dependent phase of insulin secretion, hence they only promote insulin secretion when levels of glucose are elevated. They also decrease glucagon production and gastric emptying. In addition, modified agonists target the central nervous system and have effects on GLP1 neurons that underpin the anorexiant effects of these agonists. Dual and triple agonists also affect glucose-dependent insulinotropic peptide (GIP) and glucagon receptor function, contributing to the overall glucose-lowering effect. Sodium–glucose cotransporter 2 (SGLT2) inhibitors are antihyperglycaemic agents that promote glycosuria. Combinations leveraging the different properties of these compounds are commonly used.

serine–threonine kinases phosphorylate sites on the insulin receptor itself[45] and its main substrates, inhibiting insulin signalling[46]. Assessing the effect of individual biochemical events at the organismal level is challenging. For example, phosphorylation of IRS1 on Ser-307 dampens insulin signalling in cell culture[46], but increases it in vivo, conferring protection against insulin resistance[47].

Another example of negative regulation is the mTOR-dependent, S6K-mediated phosphorylation of IRS1 on multiple serine and threonine residues, which leads to decreased function and levels of this important mediator of insulin action[48]. In addition, certain substrates exert an inhibitory effect on insulin receptor signalling. For example, GRB10 and GRB14 bind to the intracellular domain of the insulin receptor, effectively acting as pseudo-substrates and preventing its activation[49,50]. At the same time, they are also substrates for phosphatases, and stabilize the insulin signal by preventing these enzymes from accessing the insulin receptor[51,52]. In the aggregate, findings that knockout mice lacking either *Grb10* or *Grb14* are insulin-sensitive or that inhibitors of these proteins can enhance insulin sensitivity indicate that GRB10 or GRB14 are negative regulators of insulin action[53,54].

Similar function has been assigned to SOCS proteins (1, 3, 6 and 7), which inhibit insulin signalling either by acting as pseudo-substrates of the insulin receptor or by targeting IRS proteins for degradation[55]. Different tyrosine phosphatases can dephosphorylate the insulin receptor[56] and have received attention as therapeutic targets[57]. However, evidence that they contribute to insulin resistance is scarce. PI3K lipid phosphatases such as SHP2 and PTEN[58] and AKT phosphatases such as PHLPP1 (ref. 59) are equally important in terminating insulin action. Rather than presenting a compilation of all possible permutations of phosphatases and serine–threonine kinases, it is useful to conceptualize the termination signals as constitutive and redundant. In other words, unlike the 'on' signal, which is triggered by a single event (insulin binding to its receptor), the 'off' signal is a poised combination of many termination signals that can accrue stoichiometric advantage over the 'on' signal. A more important question, in our view, is how this clean break between the 'on' and 'off' signals is blurred by insulin resistance.

Insulin signalling is pleiotropic

If we delve more deeply into the insulin signalling pathway, its complexity and combinatorial potential for altered regulation at a large number of steps becomes apparent. For example, although deletion of the genes encoding the three FOXO isoforms has profound effects on insulin regulation of gene expression[30,31], several alternative pathways contribute to this process[60]. A hepatocyte expresses approximately 1,200 transcription factors[61], many of which can be regulated by insulin[62]. Examples include FOXK1 and FOXK2, which regulate muscle

glycolysis and hepatic glucose output in response to insulin[63,64]. The homeobox-binding protein TOX4 regulates hepatic lipid homeostasis in an insulin receptor-independent manner[65]. Each constituent of the insulin signalling pathway has multiple regulatory sites undergoing different post-translational modifications, as well as different isoforms, cellular distribution and tissue distribution[24]. With advances in mass spectrometry[66], thousands of altered phosphorylation sites have been detected in tissues and cells from patients with T2DM, although the main disruptions cluster around the canonical signalling nodes described in the section 'Introduction to insulin signalling'[67]. These modifications can occur in combinatorial arrangements not only in the same cell type, but also in an integrated physiological manner, quickly becoming a veritable maze in which the investigator can get lost. It logically follows that desensitization to insulin could occur in a heterogeneous fashion, even in the same individual at different times in their clinical history and at different tissue sites, in light of the protean features of insulin resistance. Thus, it is unlikely that any of the copious mechanisms reported in the literature[68] represent a unifying theory of the disease; rather, they underscore its heterogeneity.

Early-onset versus late-onset, direct versus indirect actions of insulin

Once insulin is released from β-cells, it binds to the receptor and activates signalling pathways in the target cell. This event occurs within minutes and requires subnanomolar concentrations of insulin[60]. As a result of the acute activation of signalling pathways, substrate fluxes are modified and secondary or indirect effects take place, owing to allosteric enzyme regulation[69], release of hormones and metabolites[70,71], as well as activation of signalling pathways that indirectly regulate insulin action[72]. In the past decade, a false dichotomy between direct effects and indirect effects of insulin has taken over the debate on insulin resistance. The two modes of action are both necessary and seamlessly integrated to maintain euglycaemia[73,74]. It follows from the discussion of hyperinsulinaemia-induced receptor downregulation that in insulin-resistant states the direct actions of insulin can be impaired, leading to a more prominent role for indirect actions[75].

Two other key features of in vivo insulin action are also often overlooked for the sake of reductionism: dose-dependence and time course. A doubling of levels of insulin can, within minutes, inhibit hepatic glucose production in vivo in dogs[76]. This observation is consistent with the rapid effect of subnanomolar insulin concentrations on isolated liver, adipose tissue and muscle, which promote glycogen storage and glucose uptake and inhibit glucose production and lipolysis[77]. Evidence in dogs suggests that the direct effects of insulin predominate regardless of the route of insulin infusion, indicating that they are not a result of portal hyperinsulinaemia[78]. On the other hand, stimulation of hepatic lipogenesis is a slower process than the inhibition of hepatic

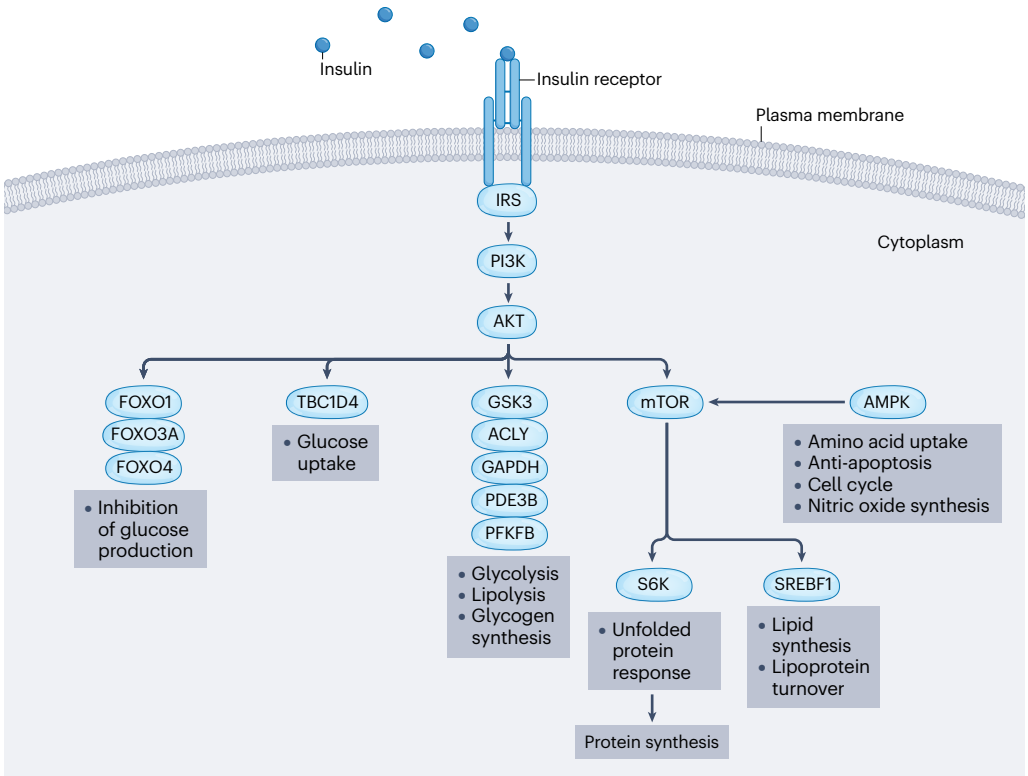

Fig. 2 | Insulin signalling. Insulin binding to the receptor triggers a conformational change that activates the receptor's tyrosine kinase. Numerous substrates are phosphorylated by the insulin receptor kinase, the most prominent and best characterized of which are the four insulin receptor substrate (IRS) proteins. They bind to phosphoinositide 3-kinase (PI3K), activating its lipid kinase activity. This action in turn leads to activation of AKT family kinases. AKT isoforms have a central role in insulin action through their many substrates, some of which are depicted here, along with the physiological actions of insulin that they mediate. Additional signalling pathways, such as the MAP kinase pathway, are thought to be involved in mediating the growth signals of insulin. ACLY, ATP citrate lyase; FOXO, forkhead box O; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GSK3, glycogen synthase kinase 3; mTOR, mammalian target of rapamycin; PDE3B, phosphodiesterase 3B; PFKFB, 6-phosphofructo-2-kinase; S6K, S6 kinase; SREBF1, sterol regulatory element-binding transcription factor 1; TBC1D4, TBC1 domain family member 4.

glucose production and requires higher insulin doses[79]. Conversely, when hepatic glucose production is measured by glucose tracing in hyperinsulinaemic clamps as opposed to pyruvate tolerance tests or in primary hepatocytes, the study design is more suited to detect indirect actions of insulin due to substrate fluxes. In other words, measurements of insulin receptor phosphorylation and activation of insulin signalling or changes in gene expression after hyperinsulinaemic clamps are generally muted[75], and are therefore poorly suited to assess rapid-onset signalling events[80]. The conclusion is that different experimental approaches must be deployed to address different questions, and conclusions reached using a single approach cannot capture the physiological entirety of insulin action.

Progression of insulin resistance

In individuals predisposed to T2DM, insulin resistance is fairly stable, whereas β-cell failure worsens rapidly as a function of rising glycaemia[81]. Age-dependent progression of insulin resistance results primarily from increased adipose tissue, independent of changes in body weight[82,83]. In contrast to insulin resistance, β-cell function deteriorates rapidly in response to modest elevations of glycaemia but rapidly recovers if glycaemia is lowered[84,85]. Thus, the β-cell response deteriorates steeply with the onset of hyperglycaemia[86]. Hyperglycaemia also contributes to decreased insulin sensitivity; this effect is known as 'glucose toxicity' and is independent of hyperglycaemia's deleterious effects on β-cell function[87]. These effects seem to be mostly attributable to glycation of effector molecules that are important for insulin signalling and to be reversible with improved glucose control[88].

The role of hyperinsulinaemia in the many diabetes mellitus subphenotypes

Cohort studies indicate that fasting hyperinsulinaemia is present in a majority of individuals with clamp-demonstrated insulin resistance and correlates with their propensity to develop diabetes mellitus[1]. Not all people with prediabetes have hyperinsulinaemia, and not all individuals with hyperinsulinaemia progress to T2DM[3]. Nonetheless, alternative biomarkers of insulin resistance, such as branched chain amino acids, atherogenic lipoproteins, free fatty acids, inflammation and cytokines, are dependent covariables of insulinaemia[89]. Therefore, given the mechanistic link with insulin signalling illustrated in the section 'Progression of insulin resistance', hyperinsulinaemia provides a window into disease pathogenesis and progression.

Is hyperinsulinaemia primary or secondary to insulin resistance?

Invoking hyperinsulinaemia as the main cause of insulin resistance begs the question of what causes hyperinsulinaemia. Again, rather than a pedantic compilation of all possible mechanisms described in the literature, the conceptual underpinnings of this question should be reviewed. First, given the complexity of the signalling interactions triggered by insulin, it is likely that the causes are heterogeneous and intertwined with the genetic determinants of T2DM[8]. Second, in cultured cells or in vivo, insulin receptor downregulation in response to hyperinsulinaemia occurs rapidly[4]. Therefore, demonstrating a mechanistic antecedent to hyperinsulinaemia in the progression of insulin resistance in the intact organism is a difficult task. When mice are rendered genetically haploinsufficient for the insulin receptor, mimicking a state of receptor downregulation, hyperinsulinaemia is detected early[90], as it is in young people with T2DM[91,92]. This factor complicates the search for mechanistic antecedents of hyperinsulinaemia.

Altered balance of insulin signalling as a result of hyperinsulinaemia

In our view, whether hyperinsulinaemia contributes to impaired insulin signalling or is simply a marker of insulin resistance is a more important consideration than the mechanistic cause of hyperinsulinaemia.

Box 1 | Overview of insulin signalling

Insulin acts at the cellular level through a single membrane-spanning receptor tyrosine kinase. The receptor recruits adaptor molecules called insulin receptor substrates to activate the lipid kinase phosphoinositide 3-kinase, which in turn activates the serine–threonine kinase AKT. AKT substrates mediate the actions of insulin on protein synthesis through additional kinases (such as mTOR), transcription factors (such as FOXO proteins and SREBF1), GLUT4 translocation (mediated by TBC1D4) and glycolytic, glycogen-synthesizing and lipogenic enzymes. Examples of these enzymes include but are not limited to glycogen synthase kinase 3, acetyl CoA lyase, glyceraldehyde phosphate dehydrogenase, phosphodiesterase and phosphofructokinase. AKT substrates also influence the cell cycle and have anti-apoptotic functions. Insulin signalling is short-lived, although its effects can be lasting.

Termination of insulin signalling is achieved primarily by internalization of the insulin–insulin receptor complex in specialized clathrin-coated pits. Although the receptor can continue to function to some extent after internalization, its active state is terminated by a combination of tyrosine phosphatases (such as PTPN1), pseudo-substrates (GRB10 and GRB14), and inhibitory serine–threonine kinases (IKKs, JNK and PKC). Such protein products are extremely redundant, ensuring that the process is efficient. Other components of the signalling pathway are also subject to inactivation by the serine–threonine kinases IKKs, JNK and PKC, lipid phosphatases (PTEN and SHP2) and serine–threonine phosphatases (PHLPP1 and PP2A). Insulin resistance is a heterogeneous process and can arise as a result of disruptions in any step of these integrated pathways. The earliest recognizable abnormality of the insulin resistant state is a rise in plasma levels of insulin. Regardless of whether it is primary or secondary, hyperinsulinaemia impairs insulin signalling by causing downregulation of insulin receptors and reduced sensitivity to insulin. However, not all pathways become desensitized to insulin to the same extent. In this way, hyperinsulinaemia itself becomes a contributor to the transition from euglycaemic insulin resistance to hyperglycaemia and its complications.

FOXO, forkhead box O; GLUT4, glucose transporter 4; GRB, growth factor receptor bound protein; IKK, IκB kinase; JNK, c-Jun amino-terminal kinase; mTOR, mammalian target of rapamycin; PHLPP1, PH domain and leucine-rich repeat protein phosphatase 1; PKC, protein kinase C; PP2A, protein phosphatase 2A; PTEN, phosphatase and tensin homologue; PTPN1, protein tyrosine phosphatase non-receptor type 1; SHP2, SH2-containing protein tyrosine phosphatase 2; SREBF1, sterol regulatory element-binding transcription factor 1; TBC1D4, TBC1 domain family member 4.

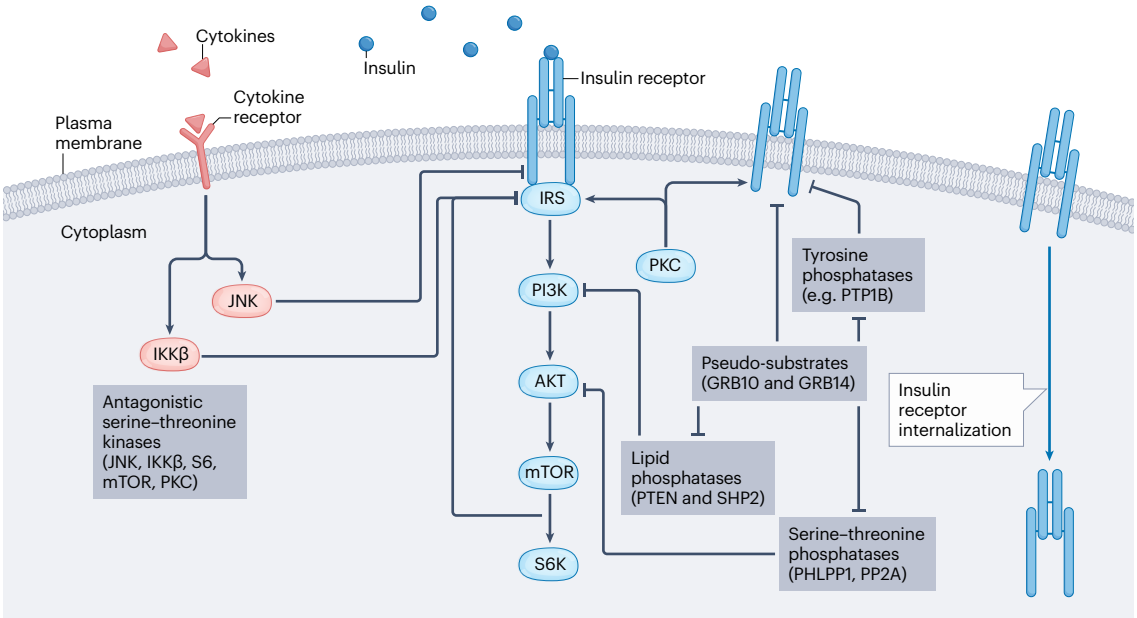

Fig. 3 | Termination of insulin signalling. The main mechanisms by which insulin signalling is terminated are illustrated. First, as the receptor is internalized into clathrin-coated pits, it becomes less accessible to substrates that localize to the plasma membrane, such as insulin receptor substrate (IRS) and phosphoinositide 3-kinase (PI3K). Similarly, serine–threonine kinases, such as AKT, target substrates that are located in different subcellular organelles, such as mitochondria and nuclei. Therefore, subcellular localization and the resulting spatial constraints are key factors in determining signal specificity and its termination. Tyrosine phosphatases inactivate tyrosine kinases; for example, protein tyrosine phosphatase non-receptor type 1 (PTP1B) inactivates the insulin receptor and the insulin-like growth factor receptor lipid phosphatases, such as phosphatase and tensin homologue (PTEN), terminate the engagement of PI3K; several serine–threonine kinases promote inhibitory phosphorylation of sites on the insulin receptor itself and its main substrates. Pseudo-substrates antagonize both forward and inhibitory signalling. For example, GRB10 can bind to the intracellular domain of the insulin receptor to prevent its activation, but can also bind phosphatases and prevent them from accessing the insulin receptor, thus strengthening the signal. GRB, growth factor receptor bound protein; IKKβ, inhibitor of nuclear factor-κB kinase subunit β; JNK, c-Jun amino-terminal kinase; mTOR, mammalian target of rapamycin; PHLPP1, PH domain and leucine-rich repeat protein phosphatase 1; PKC, protein kinase C; PP2A, protein phosphatase 2A; S6K, S6 kinase; SHP2, SH2-containing protein tyrosine phosphatase 2.

We favour a mechanism of disease in which hyperinsulinaemia gradually transitions from being a marker of disease to exerting adverse effects of its own (Fig. 4).

There are different theories that could explain such a mechanism. For example, hyperinsulinaemia might promote insulin signalling through receptors other than the insulin receptor, namely insulin-like growth factor 1 (IGF1) receptors. This mechanism is, in our view, unlikely. The levels of insulin normally detected in common insulin-resistant states cannot activate IGF1 receptors, as insulin's affinity for IGF1 receptors is >100-fold lower than its affinity for the insulin receptor[93]. The only exceptions are rare patients with extreme forms of insulin resistance, in whom levels of insulin can be up to >1,000-fold higher than normal[94]. At these levels, insulin can promote some of the phenotypic features of syndromes in these patients, including acanthosis nigricans, hyperandrogenism and cancer[94]. Equally unlikely is the possibility of actions through hybrid insulin–IGF1 receptors[95]. Insulin receptors and IGF1 receptors are assembled as homodimers co-translationally. For hybrid receptors to form in vivo, the nascent polypeptides would have to be released into the endoplasmic reticulum (ER) at the same time. Hybrid receptors can form in transfected cells that have been engineered to co-express high levels of both receptors; hybrid receptors can also be reconstituted in a test tube[96], but whether hybrids occur in vivo at the functional levels required to alter insulin action remains unclear.

Does hyperinsulinaemia skew insulin signalling?

A more relevant possibility than those described in the preceding section is that hyperinsulinaemia contributes to disease progression by both qualitative and quantitative changes in insulin signalling[97] (Fig. 4). Initial evidence for this process arose from studies of anti-insulin receptor antibodies obtained from patients with autoimmune extreme insulin resistance, which showed that the antibodies mimicked insulin action and caused downregulation of insulin receptors, but had differential effects on glucose transport versus glucose oxidation[98]. In this context, hyperinsulinaemia-induced receptor downregulation can cause differential tissue-specific and cell type-specific effects due to the different insulin sensitivities of different biological actions in different tissues[99]. For example, in adipocytes, hyperinsulinaemia results in differential effects on GLUT4 translocation versus FOXO1 nuclear exclusion, with the latter remaining sensitive to insulin after hyperinsulinaemia-induced receptor downregulation, while the former is impaired (Fig. 5a). This effect leads to decreased glucose uptake but preserved inhibition of lipolysis[100]. The differing effects of insulin resistance on lipid metabolism versus glucose metabolism underpins the McGarry hypothesis[101]. This hypothesis postulates that hyperinsulinaemia can promote muscle glucose uptake but increases free fatty acid delivery to liver and muscle, which in turn can increase glucose production in the liver and decrease glucose utilization in the muscle[101]. Although mechanistically attractive and supported by

many subsequent studies, this hypothesis does not explain what causes hyperinsulinemia in the first place.

Another example of altered insulin action under hyperinsulinaemic conditions is the dual regulation of glucose-6-phosphatase versus glucokinase in the liver (Fig. 5b). Both enzymes are exquisitely sensitive to transcriptional regulation by insulin through FOXO1: glucose-6-phosphatase is suppressed while glucokinase is activated[102,103]. Thus, as levels of insulin rise in response to insulin resistance, FOXO1 is inhibited, which results in suppression of glucose-6-phosphatase and activation of glucokinase. The pathophysiological result is suppression of hepatic glucose production and a possible increase in the amount of carbon available for lipogenesis (owing to increased glucokinase activity)[104]. This increase in available carbon provides more substrate for lipoprotein synthesis and secretion in the form of atherogenic lipoproteins. This chain of events can explain why, even in the preclinical phase of T2DM, levels of triglyceride are elevated. Regardless of which specific theory one espouses (and they are all likely to occur in vivo), the key conclusion is that hyperinsulinaemia is not only a marker of disease, but actively contributes to it by giving rise to qualitative alterations of insulin signalling, such as those described in this section.

Hormonal correlates of hyperinsulinaemia

Hyperinsulinaemia does not occur in a vacuum. Counterregulatory hormones affect the outcome of insulin resistance. People with T2DM (and people with type 1 diabetes mellitus, although this disease is not relevant to this discussion) show evidence of increased glucagon 'tone', which might account in part for insulin resistance[105]. An illustrative example of this process is the regulation of glucose production versus lipid production in the liver. When the competing effects of insulin and glucagon are analysed in the isolated, perfused rodent liver, the addition of low nanomolar concentrations of insulin is sufficient to inhibit maximal glucagon-induced glucose production[106]. This effect is due to inhibition of glycogenolysis mediated by phosphorylation and nuclear exclusion of FOXO1 (ref. 31). The roles are reversed with regard to regulation of hepatic lipogenesis. Here the effect of insulin requires high nanomolar doses and a longer time course (hours as opposed to minutes), which is consistent with the requirement for stimulation of SREBF1 synthesis and maturation[79]. In this instance, glucagon is dominant over insulin[79]. Interestingly, the ability of glucagon to promote hepatic lipid mobilization and amino acid turnover might underlie the beneficial clinical effects of moderate glucagon receptor agonism seen with triple glucagon-like peptide 1 (GLP1)–glucose-dependent insulinotropic polypeptide (GIP)–glucagon receptor (GCGR) agonists[107]. Therefore, the relative state of counterregulation is an important determinant of the pathophysiological effects of insulin resistance.

Emerging mechanistic antecedents of hyperinsulinaemia

Primary hyperinsulinaemia

Hyperinsulinaemia is probably heterogeneous and can be arrived at in different ways (Fig. 6). Insulin is cleared by receptor-mediated and non-receptor-mediated mechanisms, and the former occurs primarily in the liver but also in other tissues. A failure of insulin clearance can cause insulin resistance[2,108], and can be triggered by free fatty acids released from the expanded adipose depots of patients with obesity[109]. This mechanism can integrate the role of free fatty acids with the pathogenesis of insulin resistance[110] as well as hepatic lipid accumulation and fibrosis in metabolic dysfunction-associated fatty liver disease (also known as metabolic dysfunction-associated steatotic liver disease or non-alcoholic fatty liver disease)[111]. However, demonstrating that decreased insulin clearance can precede insulin resistance suffers from the same limitations described for hyperinsulinaemia.

Hyperreactivity of β-cells

Studies in individuals with a genetic predisposition to T2DM have indicated that an exaggerated insulin response to nutrients is an early feature of disease progression[112]. However, dissecting the extent to which nutrient-induced hyperinsulinaemia is merely a reflection of peripheral insulin resistance versus intrinsic hyperreactivity of β-cells is difficult[113]. Moreover, physiological insulin secretion in response to meals in humans has at least two distinct phases, which correspond to different cellular mechanisms of insulin synthesis, processing and secretion[114]. Therefore, a qualitative defect, rather than a quantitative defect in the integration of these phases can result in a mismatch between plasma levels of insulin and physiological insulin requirements to yield hyperinsulinaemia[115].

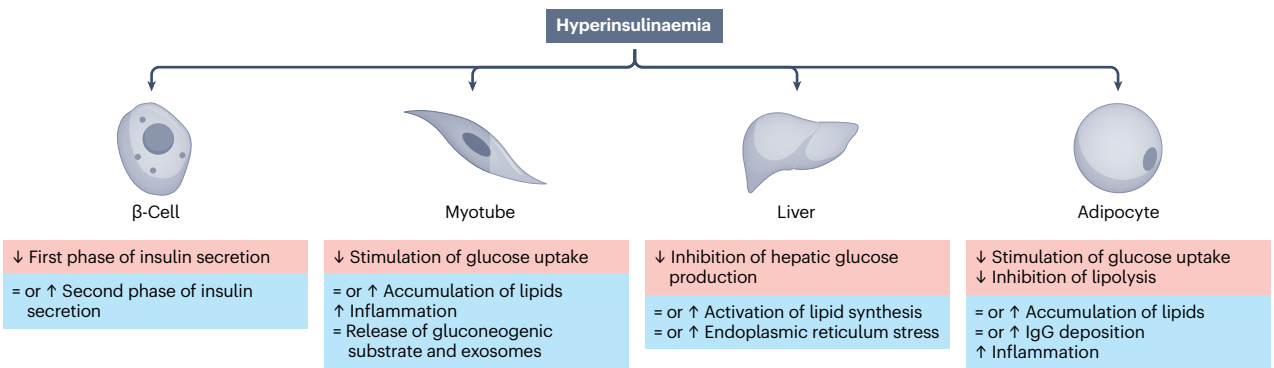
Hyperinsulinaemia
β-Cell
Myotube
Liver
Adipocyte
↓ First phase of insulin secretion
= or ↑ Second phase of insulin secretion
↓ Stimulation of glucose uptake
= or ↑ Accumulation of lipids
↑ Inflammation
= Release of gluconeogenic substrate and exosomes
↓ Inhibition of hepatic glucose production
= or ↑ Activation of lipid synthesis
= or ↑ Endoplasmic reticulum stress
↓ Stimulation of glucose uptake
↓ Inhibition of lipolysis
= or ↑ Accumulation of lipids
= or ↑ IgG deposition
↑ Inflammation

Fig. 4 | Hyperinsulinaemia affects insulin signalling. Hyperinsulinaemia can alter the balance of insulin action. Red boxes indicate actions of insulin that are impaired in response to hyperinsulinaemia; blue boxes indicate actions of insulin that are either preserved or increased. In β-cells, the increased demand for insulin has the dual effect of blunting first phase insulin secretion, while delaying and prolonging second phase insulin secretion. In liver, hyperinsulinaemia can lead to decreased glucose production but increased lipogenesis and atherogenic lipoprotein production. Hyperinsulinaemia can also increase endoplasmic reticulum stress in the liver. In adipocytes and myotubes, hyperinsulinaemia can blunt insulin-dependent glucose uptake while continuing to promote lipogenesis, cause inflammation and, in adipocytes, cause IgG deposition. In hyperinsulinaemia, the release of gluconeogenic substrate and exosomes from myotubes does not change.

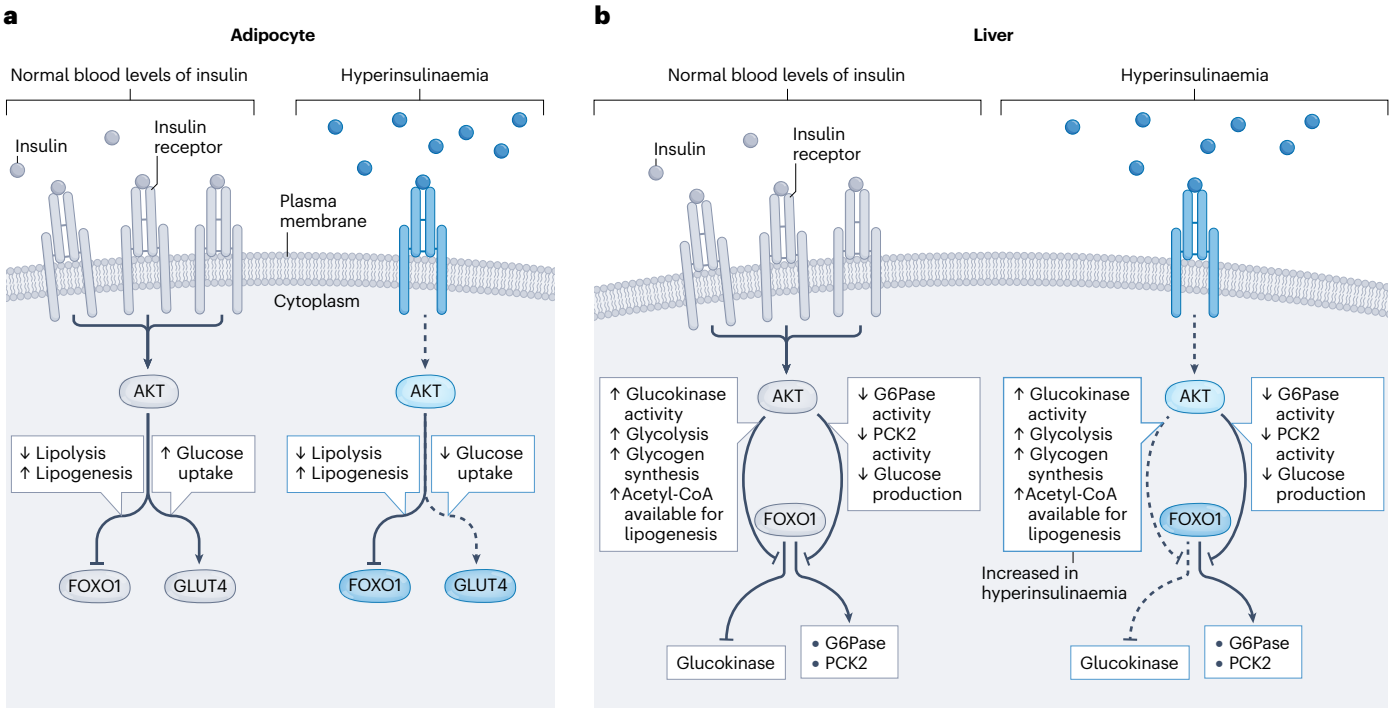

Fig. 5 | Hyperinsulinaemia uncouples insulin action on different biological responses. The sensitivity of different biological actions of insulin to hyperinsulinaemia-induced downregulation of insulin receptors differs not only between different tissues, but also within the same cell type. We provide two classic examples. **a**, In adipocytes, hyperinsulinaemia results in decreased GLUT4 translocation to the plasma membrane, thus lowering insulin-dependent glucose uptake. By contrast, insulin inhibition of FOXO1 via nuclear exclusion is preserved, leading to decreased transcription of genes regulating lipolysis, and inhibition of lipolysis. **b**, In liver, hyperinsulinaemia leads to decreased inhibition of FOXO1 by AKT. FOXO1 suppresses glucokinase and activates glucose-6-phosphatase (G6Pase) and mitochondrial phosphoenolpyruvate carboxykinase 2 (PCK2). On FOXO1 inhibition, G6Pase and PCK2 are suppressed and glucose production is decreased; however, glucokinase is activated, which results in increased carbon flux through glycolysis, increased glycogen synthesis and increased acetyl-CoA availability for lipid synthesis and lipoprotein production. This change leads to increased lipogenesis and lipid deposition in the liver, as well as increased export of atherogenic lipoproteins from the liver.

Intracellular lipids

Insulin promotes lipid synthesis and intracellular storage. Therefore, insulin resistance should in theory reduce cellular levels of lipids. This effect can occur in selected models of insulin resistance[38,116], but it is not the case in T2DM, which is often associated with increased cellular levels of lipids. Moreover, the primary consequence of increased insulin sensitivity is increased adipose tissue accumulation. The relationship between cellular levels of lipids and insulin resistance in individuals without T2DM is not linear[68,117]. Depending on the experimental model, evidence can be gathered to support the view that lipid accumulation is a cause or a consequence of insulin resistance.

Increased formation of diacylglycerol (DAG) can cause insulin resistance through activation of atypical forms of protein kinase C (PKC)[68]. PKCε phosphorylates the insulin receptor on threonine 1160 and dampens its kinase activity, resulting in insulin resistance. Loss of this phosphorylation site protects mice against diet-induced insulin resistance[45]. However, the balance of the evidence does not support the association of hepatic DAG content or activation of PKC and insulin resistance[118]. In humans, mutations leading to hepatic DAG accumulation, such as in *PNPLA3* and *ATGL*, are not associated with insulin resistance[119]. It is possible that intracellular localization of excess lipids, their chemical structure and turnover, or differences in experimental species and models underlie these discrepancies[117]. It also remains to be seen whether this mechanism occurs in other tissues (for example, skeletal muscle). Although there is a clear correlation between diet and muscle lipid content, the correlation with insulin sensitivity is complex[120], as illustrated by the so-called 'athlete's paradox' in which trained athletes display elevated muscle lipid content despite their insulin sensitivity[121].

Ceramides and fatty acids have likewise been implicated as mechanistic antecedents of insulin resistance and a range of its quantitative traits[122]. Initially, ceramides were found to be inhibitors of AKT and GLUT4 translocation[123], potentially contributing to the dissociation between the effects of insulin on glucose uptake versus lipolysis in adipocytes[100]. Subsequently, genetic or pharmacological inhibition of ceramide synthesis was found to ameliorate different metabolic conditions, including T2DM, atherosclerosis and hypertension, thus expanding the knowledge of the role of this pathway[122]. However, several studies found normal levels of ceramide in people who were insulin resistant and had T2DM, and suggested that the mechanism by which ceramide inhibits insulin action does not involve skeletal muscle and requires targets other than AKT[124].

Can lipid accumulation, brought about by factors such as inflammation or cytokines, cause insulin resistance? The main argument to support the causative role of intracellular lipids in insulin resistance is that among patients with insulin resistance, those with mutations in the

gene encoding the insulin receptor do not have increased lipoproteins and lipogenesis, whereas those with mutations in genes that encode proteins downstream of the insulin receptor (for example, *AKT2*) do[38]. This observation is consistent with the absence of lipid accumulation in the liver of mice lacking hepatic insulin receptors[116]. These data suggest that intracellular lipid accumulation occurs at a step after the insulin receptor, independent of insulin receptor downregulation or hyperinsulinaemia. The interpretation of the human genetic data should be tempered, in our view, by acknowledging the following points. First, differences in lipogenesis between patients with insulin receptor mutations versus those with *AKT2* mutations are quantitative rather than qualitative, meaning that whereas an insulin receptor mutation increased lipogenesis about twofold over controls, an AKT2 mutation increased it about threefold. Therefore, this difference does not exclude a receptor-dependent mechanism of lipid accumulation[38]. Second, the pathophysiology of insulin receptor gene mutations differs considerably from that of T2DM[94]. Third, *Akt2* knockout in mice also prevents hepatic lipid accumulation[125,126], whereas constitutive insulin sensitivity brought about by triple *Foxo* knockout leads to lipid accumulation[30,127,128]. The last two findings support the view that lipid accumulation results from a selective effect of insulin resistance on lipid metabolism. We favour the view that insulin resistance causes lipid accumulation because the lipogenic branch of insulin signalling displays a different sensitivity to insulin than does the branch of insulin signalling that controls glucose metabolism. The involvement of different intracellular signalling pathways (for example, the FOXO pathway versus the mTOR pathway) is one reason for these differences in sensitivity. It is possible that in some individuals, lipid accumulation reflects a disruption downstream of the insulin receptor and is a cause rather than a consequence of insulin resistance.

Inflammation and ER stress

Low-grade inflammation can cause insulin resistance associated with obesity and T2DM[129]. Several observations have linked different cytokines to impaired insulin signalling, primarily through the activation of antagonistic serine–threonine kinases. For example, in *Tnf*-knockout mice, protection from insulin resistance was associated with preserved insulin receptor phosphorylation and normal levels of insulin[130]. This finding suggests that TNF signalling normally antagonizes insulin signalling by way of JNK phosphorylation, and that inhibiting TNF signalling can restore insulin sensitivity[130]. Several cytokines, such as IL-6, acting through different kinases (such as IKK, JNK, S6K and PKC) have been similarly implicated[131]. During the past decade, interest has shifted to the immune cell population driving insulin resistance in adipose tissue. Resident regulatory T (T_{reg}) cells in adipose tissue have a role in age-associated insulin resistance[132,133]. Profiling of adipose-resident T_{reg} cells has identified a PPARγ-expressing subpopulation as an important effector of insulin sensitivity, required for the insulin-sensitizing effect of thiazolidinediones[134], and IL-33 as a critical effector of insulin resistance[135]. However, the antigen that causes immune cells to congregate in adipose tissue is not known, and the therapeutic effectiveness of anti-inflammatory treatments against insulin resistance and T2DM is unclear[136].

The requirements for new protein synthesis associated with anabolism increase flux through the ER, and can activate the unfolded protein response and ER stress[137]. It is possible that insulin signalling, with its increased demands for protein synthesis, causes ER stress, which in turn can inhibit the insulin receptor, activate antagonistic pathways or affect mitochondrial function through mitochondria-associated ER membranes[138]. Because it can cause defects in both insulin action and insulin secretion, ER stress provides a unifying mechanism to explain the progression from euglycaemic insulin resistance to overt hyperglycaemia[139]. It remains to be determined whether ER stress is a result or a cause of insulin resistance.

Exosomes

Many cell types release extracellular vesicles that originate in the endosomal pathway and can signal to target cells in different organs. Exosome content varies and includes microRNAs (miRNAs), lipids and proteins. Initially identified as mediators of cancer spread and progression, as well as immune modulation[140], exosomes have been studied in obesity and T2DM[141]. Among cell types known to have a role in the pathogenesis of insulin resistance, adipocytes release miRNA-containing or lipid-containing exosomes that act on target cells to regulate metabolic responses[142,143]. Exosomes released by adipocytes account for a large fraction of circulating miRNAs, and their genetic ablation is associated with insulin resistance and impaired glucose tolerance that can be restored by adipose tissue transplantation[142].

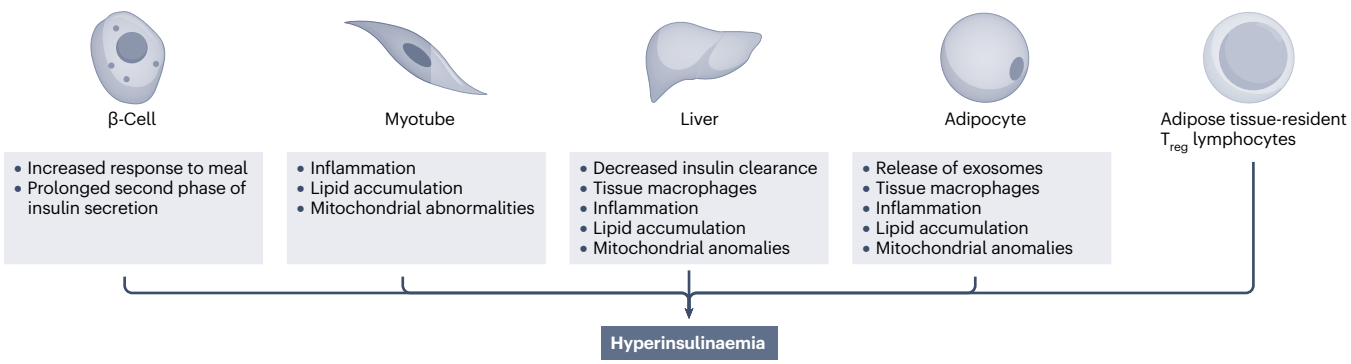

Fig. 6 | Causes of hyperinsulinaemia. Hyperinsulinaemia can occur as a result of impaired insulin clearance or excessive and/or inappropriately timed insulin secretion. Each one of these alterations in insulin secretion can occur as a primary defect in β-cell function or as a secondary effect to decreased peripheral insulin sensitivity. A subclinical level of inflammation, characterized by elevated levels of inflammatory cytokines and an absence of fever, can activate signalling pathways that inhibit insulin action. This effect can lead to or result from lipid accumulation in different tissues. Exosomes released from different cell types, such as adipocytes, can deliver miRNA and lipids that blunt insulin action. Impaired mitochondrial function, due to quantitative and qualitative abnormalities, can be linked with endoplasmic reticulum stress and the unfolded protein response as a trigger of processes leading to insulin resistance. Adipose tissue-resident T regulatory cells (T_{reg}) can also contribute to hyperinsulinaemia by promoting age-associated insulin sensitivity.

Adipose exosome-derived miRNAs can suppress plasma levels of fibroblast growth factor 21 (FGF21) and FGF21 function, mimicking certain actions of insulin-sensitizing thiazolidinediones[144]. However, whether this mechanism has a role in common forms of insulin resistance has not yet been shown. In addition, the lipids that adipocytes release through exosomes can act independently of the canonical lipolysis pathway and affect distant tissues either directly or by way of inflammatory factors or differentiation factors that regulate tissue macrophages[143].

Conversely, adipose tissue macrophages secrete exosomes that regulate adipocyte function via miRNAs, primarily mir155, which acts on PPARγ[145], and mir690, which acts on NAD kinase[146]. The role of exosomes is not limited to adipose tissue. Additional evidence suggests that exosomes released by immunocytes can influence the pro-inflammatory response associated with insulin resistance in liver and muscle[147]. There are also examples of exosomes that affect apoptosis of pancreatic β-cells, endothelial function and hepatic lipid accumulation[141].

Although the biology of exosomes and their mechanistic role in promoting insulin resistance deserve close investigation, we should reserve judgement until more evidence surfaces. A conceptual integration of how exosomes released by different cell types in different tissues can orchestrate organismal insulin resistance is needed. Similarly, it is important to understand the heterogeneous composition and content of exosomes, the factors regulating their release and the broad base of disease conditions that seem to be associated with altered exosome release and composition.

Mitochondrial function

Qualitative and quantitative mitochondrial abnormalities are commonly found in tissues of patients with insulin resistance and T2DM[148–150]. The extent to which these alterations are a product or a cause of insulin resistance remains debated. Increased lipid accumulation in skeletal muscle, as outlined in the section 'Intracellular lipids', is associated with impaired mitochondrial oxidative phosphorylation, especially in the postprandial state, a concept known as 'metabolic inflexibility'[151]. A 2014 study showed that this concept applies to β-cell dysfunction as well[152]. We addressed the role of mitochondrial abnormalities in β-cell function in a separate article published in 2023 (ref. 8). This finding contrasts sharply with the improved mitochondrial function in a mouse model of adipocyte-specific insulin receptor ablation, which suggests that the role of altered mitochondrial function is tissue-specific[153].

Multiple aspects of mitochondrial impairment have been linked to insulin resistance, including impaired fission and fusion through mitofusin[154]. An additional mechanism of impaired adipose metabolism due to mitochondrial dysfunction was reported in 2024 and involves the small Ras-GTP protein RALA, which promotes fission in a DRP1-dependent manner[155]. In light of the pleiotropic functions of mitochondria and the protean manifestations of inherited mitochondrial defects (which include dysmetabolism), the question of what mechanisms underlie the specific effects of mitochondrial impairment on insulin resistance is an intriguing one.

IgG accumulation in adipose tissue during ageing

There is a new hypothesis that the progressive deterioration of insulin action that occurs with increased adiposity during ageing in humans and experimental animal models is associated with accumulation of tissue IgG antibodies through a mechanism involving insulin receptor signalling[156]. Conversely, calorie restriction, an intervention known to improve insulin sensitivity, reduces IgG deposits. The general relevance of this mechanism remains to be determined, given the complex relationship between insulin resistance and ageing.

Challenges and therapeutic implications

Disease models fail to capture the complexity and evolution of diabetes mellitus

The reductionist approach to insulin signalling involves trying to tease out causal factors of insulin resistance from cellular and molecular studies. This approach is imperfect, as insulin has integrated functions in multiple tissues that send feedback signals to the target cells. On the other hand, in vivo measures of insulin action and tissue analyses provide an overall picture of metabolic fluxes but cannot pinpoint actionable molecular defects. Both approaches are necessary to make progress in understanding and treating the disease.

There are discrepancies between the results obtained from cellular studies, molecular studies, experimental animal studies and investigations that involve human participants. In addition, in a chronic disease such as T2DM, determining when a process starts is fraught with imponderables; data obtained using tissues and molecular determinations are necessarily snapshots, which makes it difficult to discern cause from effect. An illustrative example is the failure of studies of islets from people with T2DM to identify a shared set of genes involved in T2DM pathogenesis[157]. We should acknowledge that disease heterogeneity continues to elude our ability to document molecular signatures in different tissues, and that the clinical course of the disease affects T2DM pathophysiology, which further complicates interpretation of in vivo data. The alleged poor predictive power of animal studies with regard to efficacy and safety in humans is germane to this issue.

In spite of these limitations, it is important to note that all newly approved drugs were discovered and tested in experimental models of diabetes mellitus, and that early failures in experimental models saved time, money and lives.

Genetic and pharmacogenetic approaches to insulin resistance

Over the past two decades, an increasing number of T2DM susceptibility alleles have been identified and linked to different quantitative traits, including insulin resistance[158]. Although functional data linking specific sequence variants to the known pathophysiology of disease are only slowly emerging[159,160], there is great potential to leverage this information to improve and individualize treatment (to provide so-called 'precision' medicine), especially in the light of the increasingly complex T2DM pharmacopoeia. The limitations illustrated in the two preceding sections are intended as a cautionary note in interpreting genetic data. Gene expression and protein modification databases are isolated from one another and become rapidly obsolete, and access to curators and bioinformaticians to query and integrate clinical findings, genetic data and research advances remains haphazard[161].

Conclusions

Throughout the twentieth century, plant-derived biguanides, sulfonamides and animal insulin were the only tools available to the T2DM clinician[162]. Starting with the introduction of PPARγ agonists, there have been many additions to the T2DM pharmacopoeia, culminating with the introduction of SGLT2 inhibitors, GLP1 receptor agonists and other incretin-based drugs[163]. Insulin treatment has also made transformative progress with the production of designer insulins[164]. However, after years of improving trends in T2DM complications, data collected between 1990 and 2010 point to a resurgence in certain types of organ

damage[165]. The challenge in T2DM treatment is to devise interventions that change the progressive nature of the disease, are not subject to drug failures or reduced adherence to treatment and are widely accessible to patients, regardless of socioeconomic and cultural barriers.

In our view, although GLP1 receptor agonists and their numerous permutations are indeed game-changers, it would be shortsighted to declare victory and cease research into better T2DM treatments. There are several reasons for this assertion: GLP1 receptor agonists do not reverse the fundamental impairment of insulin action, the durability of their direct effects on β-cells is limited[166] and adherence to treatment is a challenge[14,15,167–169]. In addition, in our view of T2DM (which, admittedly, focuses on high-income countries), we tend to overlook the fact that the disease is rising at its fastest pace among populations in which overweight, the main indication for GLP1 receptor agonist use, is not as pervasive or severe as in North America and Europe, and in which a decrease in muscle mass, as brought about by GLP1 agonist-driven weight loss, is not a desirable outcome[170]. The vicious cycle of insulin resistance and β-cell dysfunction cannot be untangled without acting on both processes. The investment of research and development resources into selective insulin sensitizers such as selective PPARγ agonists[171,172], FOXO1 inhibitors[104], FGF19 and FGF21 (refs. 173,174), and germane mechanisms is limited. Paradigm-altering treatments of β-cell dysfunction targeting dedifferentiation[84,175,176], senescence[177,178] and metabolic inflexibility[179–182] have received little attention outside academic environments. We believe that these are promising areas that can lead to disease modification or reversal and should be pursued more vigorously than they currently are.

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